Research Paper

Neural correlates of recognition memory of social information in people with schizophrenia

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Background: Social dysfunction is a hallmark characteristic of schizophrenia. Part of it may stem from an inability to efficiently encode social information into memory and retrieve it later. This study focused on whether patients with schizophrenia show a memory boost for socially relevant information and engage the same neural network as controls when processing social stimuli that were previously encoded into memory. **Methods:** Patients with schizophrenia and healthy controls performed a social and nonsocial picture recognition memory task while being scanned. We calculated memory performance using d'. Our main analysis focused on brain activity associated with recognition memory of social and nonsocial pictures. **Results:** Our study included 28 patients with schizophrenia and 26 controls. Healthy controls demonstrated a memory boost for socially relevant information. In contrast, patients with schizophrenia failed to show enhanced recognition sensitivity for social pictures. At the neural level, patients did not engage the dorsomedial prefrontal cortex (DMPFC) as much as controls while recognizing social pictures. **Limitations:** Our study did not include direct measures of self-referential processing. All but 3 patients were taking antipsychotic medications, which may have altered both the behavioural performance during the picture recognition memory task and brain activity. **Conclusion:** Impaired social memory in patients with schizophrenia may be associated with altered DMPFC activity. A reduction of DMPFC activity may reflect less involvement of self-referential processes during memory retrieval. Our functional MRI results contribute to a better mapping of the neural disturbances associated with social memory impairment in patients with schizophrenia and may facilitate the development of innovative treatments, such as transcranial magnetic stimulation.

Introduction

Individuals who successfully navigate their social world greatly rely on the efficient processing of social cues from the environment. There is accumulating evidence suggesting that social information gains privileged processing to produce adaptive behaviour and serve regulatory functions for an individual in a social environment.[1] The privileged processing of social information is likely to facilitate memory encoding and retrieval, similar to the well-established modulation of memory performance by emotions.[2–6] It has been proposed that social and emotional processes have inherent connections and share basic neural mechanisms.[7] While the capacity to remember socially relevant information may partly rely on the same memory systems involved in emotional memory, evidence also suggests that memory for social information relies on specific brain regions, including the dorsomedial prefrontal cortex (DMPFC).[8,9]

It is now well known that patients with schizophrenia have difficulty processing social cues,[10–12] which likely contributes to social dysfunction.[13] Such a dysfunction is a hallmark characteristic of schizophrenia with important implications for the outcome of this illness.[14–17] Part of the social dysfunction in patients with schizophrenia may stem from an inability to efficiently encode key social information into memory and later recognize socially relevant information during social interactions. There is recent evidence showing that patients with schizophrenia do not show the typical memory boost for information processed in a socially relevant manner.[18] Few other studies on schizophrenia have directly investigated recognition memory of social compared with nonsocial stimuli.

Individuals with schizophrenia usually demonstrate significant impairment in episodic memory in general[19–21] and in recognition memory,[22] and they do not always benefit from a memory boost when they need to recognize emotional stimuli.[23–25] It is

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not clear, however, whether they can benefit or not from a memory boost for social information. It is possible that an altered memory of social information in patients with schizophrenia may be associated with abnormalities in different neural regions than those typically associated with emotional memory deficits (i.e., amygdala).[23,24] Because social stimuli are often emotionally charged, it is challenging to delineate the contribution of emotional processing to the encoding and retrieval of social stimuli from the contribution of independent and/or socially specific processes.

To partly address this challenge, we selected a series of complex emotional and neutral pictures depicting either social content or nonsocial content. Based on past studies,[7,8,26] we defined social pictures as those showing at least 1 human being, whereas the nonsocial ones were characterized by the absence of any human being. Both social and nonsocial picture categories were equated in terms of emotional content. Using these pictures, we administered a picture recognition memory task among patients with schizophrenia and healthy controls during functional magnetic resonance imaging (fMRI). The task was divided into 2 phases: a study phase during which participants categorized social and nonsocial pictures in 1 of 3 emotional valence categories and a recognition test during which participants were required to make an old or new recognition judgment on each image in a series of previously studied pictures intermixed with unstudied pictures. The innovative aspect of our protocol was the systematic manipulation of the presence of social content within the to-be-encoded pictures while maintaining equivalent emotional content across conditions.

The present study had 2 main objectives. The first was to test whether healthy controls and patients with schizophrenia demonstrate better recognition memory of social pictures than nonsocial ones. We hypothesized that contrary to healthy controls, patients with schizophrenia would not show enhanced recognition memory for social pictures compared with nonsocial ones. Our second objective was to investigate the neural correlates of recognition memory of social information in patients with schizophrenia. We hypothesized that patients would not engage the same neural network as controls when recognizing social pictures. Specifically, we expected patients to show significantly reduced activity in the DMPFC compared with controls.

Methods

Participants

We recruited patients with schizophrenia from various outpatient clinics at the Douglas Mental Health University Institute. Diagnosis was established with the Structured Clinical Interview for DSM-IV[27] conducted by trained interviewers (minimum κ of 0.75). Positive and negative symptoms were assessed with the Scale for the Assessment of Positive Symptoms[28] and the Scale for the Assessment of Negative Symptoms,[29] respectively. Exclusion criteria for patients were substance abuse or dependence in the previous 6 months, IQ less than 75 points, history of loss of consciousness for more than 1 hour and an identifiable neurologic disorder. We recruited controls through newspaper advertisements. Exclusion criteria for controls were history of schizophrenia or other psychotic disorder, bipolar disorder, recurrent depression, history of substance dependence, any substance abuse in the previous 6 months,[27] history of loss of consciousness for more than 1 hour, schizophrenia or other psychotic disorder in a first-degree relative and a significant neurologic disorder. All participants were assessed with the Wechsler Abbreviated Scale of Intelligence to estimate full-scale IQ[30] and the Rey Auditory Verbal Learning Test.[31] We evaluated patients' ability to give fully informed consent by asking them some questions about the procedure and their rights as research participants after they had read the consent form. All participants provided written informed consent, and the study was approved by the Douglas Institute institutional review board.

Picture recognition memory task

Stimuli

We used 300 colour pictures selected from the International Affective Picture System (IAPS)[32] and the Empathy Picture System (EPS)[26] for the picture recognition memory task. Stimuli were originally classified into 6 categories (50 pictures in each category): social content with positive valence, social neutral, social negative, nonsocial positive (i.e., beautiful landscapes), nonsocial neutral (e.g., household objects) and nonsocial negative (e.g., scenes of destruction).

Experimental design

The picture recognition memory task was administered in the scanner and involved 2 phases: a study phase and a yes/no recognition memory test. During the study phase, 150 pictures (50 for each valence condition; half social and half nonsocial) from pregenerated list I, II or III (counterbalanced across participants) were pseudorandomly presented 1 at a time. Each picture was presented for 3 seconds, followed by a fixation cross presented for 2 seconds. Stimulus presentations were desynchronized with respect to the onsets of volume acquisitions to increase the effective sampling rate and thus get a better estimate of the hemodynamic response.[33] Participants were required to categorize each picture into its proper emotional valence using a 3-button computer mouse. Correct answers for this valence categorization task were determined by original ratings from IAPS and EPS.[26,32] Participants were not explicitly told to remember the pictures. The study phase was directly followed by the recognition memory test. We presented 150 previously studied and 150 new pictures pseudorandomly. Again, each picture was presented for 3 seconds, followed by a fixation cross presented for 2 seconds. Participants were required to judge whether each picture had been presented during the study phase or not (old v. new). We recorded responses and reaction times. After the scanning session, participants rated the emotional valence of all pictures on a laptop computer. To get more precise and idiosyncratic valence ratings, each picture was accompanied by a continuous line with the label "very negative" at the left end of the line and the label "very positive" at the right end. Participants were told that the middle of the line was associated with neutrality. Using a

mouse, participants moved an arrow on this line and clicked the left button once the arrow was well positioned on the line according to the emotional valence of the picture. The continuous line was in fact an ordinal scale ranging from 1 to 323. We performed our statistical analysis for picture valence ratings using these values. Because we did not find any significant group difference for picture valence ratings and because the main objective of the present study was to investigate recognition memory of social information, we pooled valence conditions together to create 2 picture categories: social and nonsocial.

Imaging data acquisition

Scanning was conducted on a 1.5 T Siemens Sonata scanner at the Montreal Neurological Institute (MNI). A vacuum cushion stabilized the participant's head. Stimuli were generated by an IBM PC laptop computer running E-PRIME (Psychology Software Tools) and projected via an LCD projector and mirror system. A mouse connected to the computer recorded the participants' responses. We acquired functional T_2-weighted images with blood oxygen level–dependent contrast (repetition time [TR] 2750 ms, echo time [TE] 50 ms, flip angle 90°, field of view 256 mm, matrix 64×64), covering the entire brain (30 interleaved slices parallel to the anterior–posterior commissural plane, in-plane resolution 4×4 mm, 4 mm thickness). Three functional runs of 278 volumes each were acquired (1 for the study phase and 2 for the recognition memory test). Following the functional session, a high-resolution T_1-weighted anatomic volume was acquired using a gradient echo pulse sequence (TR 22 ms, TE 9.2 ms, flip angle 30°, voxel size $1 \times 1 \times 1$ mm^3).

Statistical analysis

Behavioural data analyses

We performed statistical tests using SPSS version 18.0. We compared demographic data between groups using Student *t* tests for independent samples, except for the sex variable, for which we used the χ^2 test. For study phase, we performed 2 (group) × 2 (social v. nonsocial) analyses of variance (ANOVA) on both accuracy (%) and reaction time at the valence categorization task. For the recognition phase, we first calculated the hit rate (i.e., proportion of old pictures correctly recognized) and false alarm rate (i.e., proportion of new pictures incorrectly identified as old pictures) for each group and condition. Recognition memory sensitivity was calculated using the Signal Detection Theory Index D-Prime (d' = Z(hit rate) − Z(false alarm rate)).[34] We then conducted a 2 (group) × 2 (social v. nonsocial) ANOVA on these performance values. We also conducted a 2 (group) × 2 (social v. nonsocial) × 2 (old v. new) ANOVA on reaction time data. Finally, a 2 (group) × 2 (social v. nonsocial) × 3 (valence) ANOVA was conducted on valence rating values to confirm the absence of group difference in perceived emotion.

Functional MRI data analyses

We analyzed fMRI data using Statistical Parametric Mapping (SPM8). All functional volumes from each run were realigned to the mean of the images to correct for interscan movement, spatially normalized to the MNI space (normalized voxel size $2 \times 2 \times 2$ mm) and smoothed with an 8 mm full-width at half-maximum Gaussian kernel.[35] Low-frequency temporal drifts were removed by applying a high-pass filter. We used an autoregressive model to estimate and correct for nonsphericity of the error covariance.[36] Data were analyzed by the general linear model in which individual events were modelled by a canonical hemodynamic response function. We performed 3 main analyses: 2 using data acquired during the recognition memory test and 1 using data from the study phase (i.e., encoding).

The first analysis explored the neural correlates of recognition memory without modelling behavioural performance. Potential group differences in brain activity for the related-contrasts may thus partly reflect, or be the result of, a memory deficit in 1 group. Four events of interest were modelled: all old social pictures, all old nonsocial pictures, all new social pictures and all new nonsocial pictures. First, within each content condition separately, we contrasted the old pictures with the new pictures to extract brain activity associated with recognition memory. Then we directly compared groups for the recognition of old social pictures versus old nonsocial pictures (i.e., old social v. old nonsocial × controls v. patients). The aim of this interaction contrast was to verify whether there were any group differences in magnitude of activity among the brain regions that were significantly more active during the recognition of social versus nonsocial pictures.

We conducted a second analysis that took into account behavioural performance to complement findings from the first analysis. We modelled 4 events: correctly identified old social pictures (social hits), correctly identified old nonsocial pictures (nonsocial hits), correctly rejected new social pictures (social CR) and correctly rejected new nonsocial pictures (nonsocial CR). This analysis provided a measure of retrieval-related activity under conditions where performance was matched across groups (i.e., successful retrieval only). In this case, potential group differences in brain activity cannot be linked to a behavioural memory deficit and may instead reflect diverse cognitive strategies or memory processes involved during successful retrieval.

To better understand and interpret the recognition memory results, we conducted a third analysis that explored the neural correlates of successful encoding using a subsequent memory effect (SME) approach. We modelled 4 events extracted from the study phase: social pictures subsequently remembered during the recognition test (social hits), nonsocial pictures subsequently remembered (nonsocial hits), social pictures subsequently forgotten (social misses) and nonsocial pictures subsequently forgotten (nonsocial misses). This analysis provided a measure of brain activity associated with successful encoding of social and nonsocial information. Because SME analyses require a number of mistakes for each condition (e.g., at least 10 mistakes) to model the "misses" events, 3 patients and 3 controls who performed too well on the task had to be excluded from this third analysis.

All analyses included 6 regressors modelling motion-related variance as covariates. We conducted 1- and 2-sample *t* tests to obtain mean activation maps. Resulting activation maps were thresholded at $p < 0.005$, with an extent threshold of 43 contiguous voxels, corresponding to a false-positive

discovery rate of less than 5% across the whole brain. This cluster size thresholding method was applied to correct for multiple comparisons, and was estimated by Monte Carlo simulation (10 000 simulations).[37] Finally, instead of presenting fMRI results for each group separately, we report results of conjunction analyses, which identified brain activations that were significantly common to both groups for a given contrast, in addition to the interaction analyses. Conjunctions analyses were performed using default SPM8 procedures.

Results

Participants

Twenty-eight right-handed patients with schizophrenia and 26 right-handed healthy controls participated in the study. Patients and controls were comparable in terms of age, education, sex ratio and IQ. Demographic, cognitive and clinical data are provided in Table 1. All patients had been clinically stable for at least 4 weeks and had been on a fixed medication regimen for at least 6 weeks. All patients except 3 were taking antipsychotic medication; 22 were taking second-generation antipsychotics and 3 were taking conventional antipsychotics (equivalent to a mean dose of 335 mg/d of chlorpromazine[38]). None of the patients had a concurrent mood disorder at the time of the study. No patients were taking benzodiazepines.

Key behavioural results

Study phase
Patients had lower accuracy for categorizing pictures than controls. Categorization accuracy was not significantly different for social versus nonsocial pictures. Reaction time during picture categorization was similar between patients and controls.

Recognition memory test
The ANOVA on recognition sensitivity data revealed a significant group × content interaction. As illustrated in Fig. 1, controls showed a significant memory boost for social pictures compared with nonsocial pictures ($p = 0.004$). In contrast, patients failed to show enhanced recognition sensitivity for social information ($p = 0.44$). Reaction time during recognition was similar between patients and controls. Participants took more time to recognize social than nonsocial pictures. They also took more time to process new pictures than old ones.

Table 1: Demographic, cognitive and clinical data of patients with schizophrenia and healthy controls

Characteristic	Group; mean ± SD*		Statistical test	*p* value
	Schizophrenia, *n* = 28	Control, *n* = 26		
Age, yr	31.0 ± 8.8	30.7 ± 9.8	$T_{52} = 0.12$	0.90
Education, yr	13.0 ± 2.6	13.8 ± 2.2	$T_{52} = 1.24$	0.22
Sex, male:female	17:11	13:13	$\chi^2_1 = 0.63$	0.43
IQ — WASI	105.4 ± 16.7	107.1 ± 15.3	$T_{49} = 0.38$	0.72
Verbal memory — delayed recall	10.6 ± 3.1	13.3 ± 2.0	$T_{46} = 0.38$	0.001
SAPS — total	14.0 ± 16.2			
SANS — total	18.7 ± 10.3			
Age at onset, yr	21.3 ± 8.6			
No. hospital admissions	2.5 ± 1.1			

SANS = Scale for the Assessment of Negative Symptoms; SAPS = Scale for the Assessment of Positive Symptoms; SD = standard deviation; WASI = Wechsler Abbreviated Scale of Intelligence.
*Unless otherwise indicated.

Valence rating
Participants rated negative pictures as significantly more negative than both neutral ($p < 0.001$) and positive pictures ($p < 0.001$). Positive pictures were also perceived as more positive than neutral pictures ($p < 0.001$). A significant valence × content interaction revealed that social negative pictures were perceived as more negative than nonsocial negative pictures ($p < 0.001$). Valence rating was similar between patients and controls.

Behavioural data and statistical test results are provided in Table 2.

Functional MRI results

Condition effects — brain activity common in both groups
Retrieval of social and nonsocial pictures: We first examined brain regions where activity was greater during observation of old social pictures than new social pictures, irrespective of participants' responses (old – new). Both groups showed increased activity in several frontal and parietal regions and in the insula, middle temporal gyrus and caudate (Table 3 and Fig. 2). Regarding nonsocial pictures, both groups had greater activity in several frontal and parietal regions and in the cingulate and caudate (Table 4). Finally, successful retrieval of social pictures was associated in both groups with significant activation in several frontal and temporal regions and in the inferior parietal gyrus and caudate (Table 5).

Social processing (old social pictures – old nonsocial pictures): Both groups had greater activity in several brain regions previously reported to be associated with emotional processing,[39] face processing[40] and social cognition[41] during the processing of

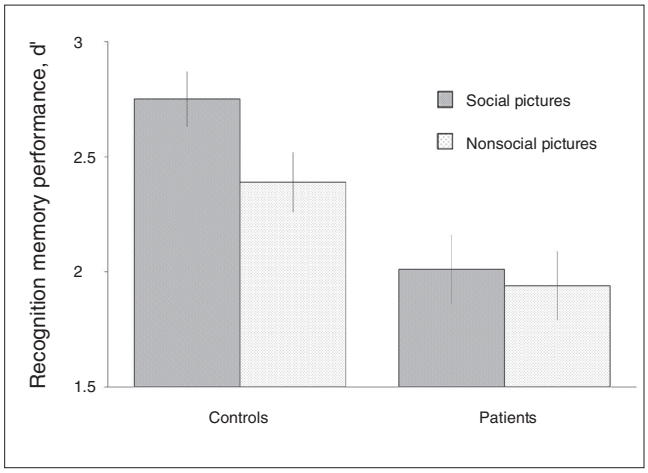

Fig. 1: Mean recognition memory performance for social and nonsocial pictures in healthy controls and patients with schizophrenia.

old social pictures compared with old nonsocial pictures. These regions include large clusters of activations in the inferior, middle and superior occipital gyri (extending to the fusiform gyri), precuneus, ventromedial PFC, dorsomedial PFC, middle temporal gyri and bilateral amygdala (Table 6).

Successful encoding of social and nonsocial pictures (hits – misses; study phase): Successful encoding of social pictures was associated in both groups with large clusters of significant activation in occipitotemporal regions (including bilateral fusiform) and in the inferior and medial frontal gyri and bilateral amygdala. Regarding nonsocial pictures, both groups showed significant activation in the inferior/middle temporal, middle occipital, fusiform and inferior/middle frontal gyri (Table 7).

Interaction effects — group differences

Retrieval of social and nonsocial pictures: Direct group comparison revealed that the activity in the DMPFC, left parahippocampal gyrus, right paracentral lobule and right superior frontal gyrus was significantly greater in controls than patients during retrieval of social pictures (old v. new; Table 3 and Fig. 3). Only the right thalamus was significantly more active in patients than controls. Regarding nonsocial pictures, the activity of the inferior and superior frontal gyri, precentral gyrus, precuneus, inferior parietal gyrus, insula, middle temporal gyrus, hippocampus and few subcortical structures was significantly greater in controls than patients. No brain region was significantly more active in patients than controls (Table 4). During successful retrieval of social information (i.e., hits v. CR), controls showed

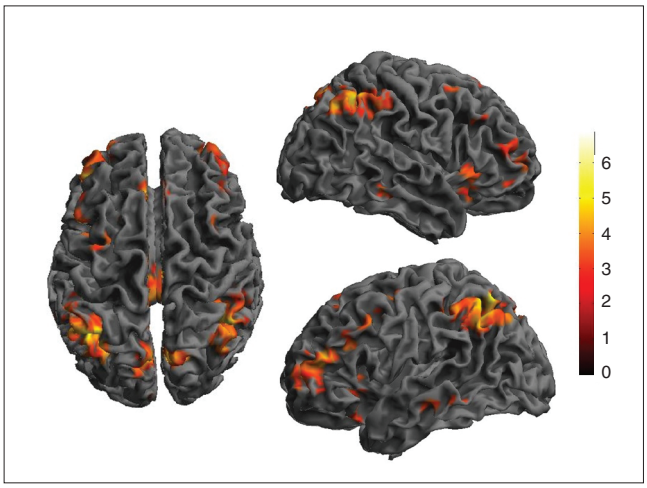

Fig. 2: Brain regions whose activity was significantly greater in patients with schizophrenia and controls during the processing of old versus new social pictures. Reported activations were thresholded at $p < 0.005$, with an extent threshold of 43 contiguous voxels, corresponding to a false-positive discovery rate of less than 5% across the whole brain. The shade bar represents t values.

Table 2: Main behavioural results of patients with schizophrenia and healthy controls

	Group; mean ± SD		Main effect of group		Main effect of content		Group × content interaction	
Study phase	Patients	Controls	F	p value	F	p value	F	p value
Valence categorization task accuracy, %			$F_{1,52} = 8.24$	0.006	$F_{1,52} = 2.89$	0.10	$F_{1,52} = 0.92$	0.34
Social pictures	79 ± 15	90 ± 11						
Nonsocial pictures	78 ± 15	85 ± 11						
Reaction time, ms			$F_{1,52} = 3.81$	0.06	$F_{1,52} = 12.80$	0.001	$F_{1,52} = 0.34$	0.56
Social pictures	1405 ± 217	1323 ± 153						
Nonsocial pictures	1365 ± 183	1267 ± 134						
Recognition test								
Memory performance, d'			$F_{1,52} = 10.39$	0.002	$F_{1,52} = 9.08$	0.004	$F_{1,52} = 4.35$	0.042
Social pictures	2.01 ± 0.77	2.75 ± 0.62						
Nonsocial pictures	1.94 ± 0.81	2.39 ± 0.68						
Reaction time, ms*			$F_{1,52} = 0.95$	0.33	$F_{1,52} = 98.48$	0.001	$F_{1,52} = 1.97$	0.17
Social old pictures	1401 ± 215	1340 ± 175						
Social new pictures	1438 ± 234	1421 ± 201						
Nonsocial old pictures	1345 ± 218	1258 ± 164						
Nonsocial new pictures	1351 ± 239	1312 ± 183						
Valence rating†			$F_{1,48} = 1.25$	0.27	$F_{1,48} = 1.57$	0.22	$F_{1,48} = 0.49$	0.49
Social neutral pictures	174 ± 18	166 ± 9						
Social negative pictures	48 ± 25	45 ± 19						
Social positive pictures	242 ± 34	238 ± 31						
Nonsocial neutral pictures	164 ± 15	158 ± 17						
Nonsocial negative pictures	71 ± 40	80 ± 23						
Nonsocial positive pictures	232 ± 38	223 ± 26						

SD = standard deviation.
*Main effect of novelty: $F_{1,52} = 8.76$, $p < 0.01$; group × novelty interaction: $F_{1,52} = 2.30$, $p = 0.14$; content × novelty interaction: $F_{1,52} = 1.95$, $p = 0.17$; group × content × novelty interaction: $F_{1,52} = 0.01$, $p = 0.95$.
†Main effect of valence: $F_{2,96} = 767.98$, $p < 0.01$; group × valence interaction: $F_{2,96} = 0.84$, $p = 0.44$; content × valence interaction: $F_{2,96} = 22.38$, $p < 0.01$; group × content × valence interaction: $F_{2,96} = 0.71$, $p = 0.50$.

significantly greater activity in the DMPFC and middle temporal gyrus than patients. Conversely, patients demonstrated greater activity in the postcentral gyrus, insula and parahippocampal gyrus (Table 5). Given the importance of the DMPFC in social memory,[8,9] we specifically graphed the parameter estimates in a cluster of activation in this brain region for each group and novelty condition (old v. new) separately to better understand and interpret the group difference (Fig. 4).

Social processing: Only the dorsomedial PFC was significantly more active in controls than patients during the processing of social pictures. Conversely, patients showed greater activity than controls in the precuneus, middle occipital gyri and postcentral gyrus (Table 6).

Successful encoding: Controls showed significantly greater activity in the cingulate, precentral, thalamus and inferior frontal gyrus than patients during successful encoding of social information. Conversely, patients demonstrated greater activity in the middle frontal and supramarginal gyri. For the successful encoding of nonsocial pictures, controls showed greater activity than patients in the inferior parietal, precentral, superior temporal and middle occipital gyri and in the hippocampus (Table 7).

Correlations between DMPFC activity and recognition memory performance

We extracted, for each participant, the parameter estimates of brain activity in the DMPFC during retrieval of old social pictures and correlated the activity with recognition memory performance for social pictures. Neither controls ($r = 0.38$, $n = 26$, $p = 0.06$) nor patients ($r = 0.11$, $n = 28$, $p = 0.57$) showed a significant correlation between DMPFC activity and memory performance. A trend was nonetheless observed for controls.

Discussion

An inability to effectively encode and recognize socially relevant information may partly explain social dysfunction in patients with schizophrenia. Few studies, however, have explored episodic memory for social information in this

Table 3: Results of the conjunction and interaction analyses for recognition of social information (i.e., old social pictures v. social new pictures)*

Analysis; brain region	Talairach coordinates			*t* value	Cluster size
	x	*y*	*z*		
Conjunction†					
Left hemisphere					
Inferior parietal lobule (BA 7,40)	–30	–55	43	6.35	1718
Precuneus (BA 7)	–6	–70	37	5.82	2905
Middle frontal (BA 46)	–39	38	16	4.76	903
Middle temporal gyrus (BA 21)	–61	–29	–8	4.73	85
Medial PFC (BA 8)	–3	30	47	4.53	818‡
Caudate	–11	5	8	4.32	204
Middle frontal (BA 8)	–49	15	39	4.15	224
Insula (BA 13)	–29	17	6	3.75	283
Right hemisphere					
Inferior parietal lobule (BA 40)	43	–51	41	5.43	1537
Caudate	9	11	1	5.19	191
Insula (BA 13)	30	17	–7	4.87	372
Medial PFC (BA 32,10)	5	35	13	3.89	818‡
Middle frontal (BA 10)	33	53	6	4.20	468
Middle temporal gyrus (BA 21)	55	–37	–5	3.82	110
Interaction					
Controls > patients					
Left hemisphere					
Parahippocampal gyrus (BA 35)	–17	–29	–6	4.36	69
Right hemisphere					
Medial frontal/frontal pole (BA 10)	19	59	17	5.62	188
Paracentral lobule (BA 31)	2	–21	42	3.89	71
Superior frontal (BA 6)	21	28	32	3.87	87
Patients > controls					
Right hemisphere					
Thalamus	17	–30	5	3.60	54

BA = Brodmann area; PFC = prefrontal cortex.
*The cluster size represents the number of voxels. Talairach coordinates represent the peak voxel of each cluster where *x*, *y*, and *z* indicate the distance measured in millimetres from the anterior commissure in the sagittal, coronal and horizontal planes, respectively. All clusters of activation were significant at $p < 0.005$, uncorrected for multiple comparisons, with a minimum cluster size of 43 contiguous voxels, corresponding to a false-discovery rate of less than 5% across the whole brain as estimated by Monte Carlo simulation.
†The *t* value reported for the conjunction analysis corresponds to the lowest *t* value between the groups.
‡These peak voxels belong to the same cluster of activation.

population. Our objectives focused on whether patients with schizophrenia benefit from a memory boost for socially relevant information and whether they engage the same neural network as controls when observing social stimuli that have been previously encoded into memory. At the behavioural level, healthy controls demonstrated a memory boost for socially relevant information. In contrast, patients with schizophrenia failed to show enhanced recognition sensitivity for social pictures. At the neural level, patients did not engage the DMPFC as much as controls while observing and recognizing social pictures that were previously encoded.

In line with the results of previous studies, controls had better overall recognition memory than patients, regardless of condition (i.e., social vs. nonsocial).[23,42,43] As hypothesized, controls showed enhanced recognition memory for pictures depicting social content compared with nonsocial pictures. This enhanced memory effect is analogous to the well-established memory boost for emotional stimuli compared with neural ones.[2–6] Late long-term potentiation in medial temporal regions is modulated by activity from brain regions (e.g., amydgala, prefrontal cortex) involved in detection and assessment of emotional stimuli.[44–47] Given that the neural mechanisms underlying social and emotional information processing are highly interconnected,[7,48] similar modulatory processes may be involved during memory encoding and recognition of social stimuli. One could suggest that we observed a memory boost for social pictures simply because these pictures are more emotionally charged than nonsocial pictures. This is unlikely, however, because our paradigm allowed us to control for the emotional content by equating the number of emotional pictures within social and nonsocial picture conditions. The ANOVA on valence rating data did not show a significant main effect of content ($p = 0.22$), suggesting that perceived emotion was comparable between social and nonsocial pictures. The memory boost for social pictures may be explained by different modulatory processes that are more specifically involved in social memory.

Table 4: Results of the conjunction and interaction analyses for recognition of nonsocial information (i.e., old nonsocial pictures v. new nonsocial pictures)*

	Talairach coordinates				
Analysis; brain region	*x*	*y*	*z*	*t* value	Cluster size
Conjunction†					
Left hemisphere					
Inferior frontal (BA 10)	–38	50	–1	4.84	323
Inferior parietal lobule (BA 40)	–42	–55	45	4.53	831
Medial frontal (BA 6)	–2	32	35	4.00	141
Inferior frontal (BA 13)	–31	10	–7	3.57	69
Caudate	–10	5	9	3.34	56
Right hemisphere					
Precuneus (BA 7)	10	–68	40	5.59	1073
Supramarginal (BA 40)	40	–45	34	4.81	677
Cingulate	4	–17	30	4.17	297
Middle frontal (BA 10)	35	60	11	3.62	134
Caudate	13	2	16	3.50	53
Interaction					
Controls > patients					
Left hemisphere					
Middle temporal (BA 39)	–58	–61	10	4.67	405
Globus pallidus	–12	–4	–5	4.31	79
Inferior frontal (BA 45)	–40	19	9	4.18	160
Hippocampus	–36	–12	–15	3.91	179
Insula (BA 13)	–39	10	3	3.58	46
Putamen	–17	1	8	3.50	44
Right hemisphere					
Precentral (BA 9)	35	9	37	4.28	67
Precuneus (BA 31)	14	–53	29	3.78	148
Superior frontal (BA 6)	8	14	56	3.74	74
Superior parietal (BA 7)	21	–67	53	3.65	56
Inferior parietal lobule (BA 40)	41	–37	44	3.50	74
Precentral (BA 44)	53	16	7	3.34	51
Patients > controls					
No significant activation					

BA = Brodmann area.
*The cluster size represents the number of voxels. Talairach coordinates represent the peak voxel of each cluster where x, y and *z* indicate the distance measured in millimetres from the anterior commissure in the sagittal, coronal and horizontal planes, respectively. All clusters of activation were significant at $p < 0.005$, uncorrected for multiple comparisons, with a minimum cluster size of 43 contiguous voxels, corresponding to a false-discovery rate of less than 5% across the whole brain as estimated by Monte Carlo simulation.
†The *t* value reported for the conjunction analysis corresponds to the lowest *t* value between the groups.

In this study, memory retrieval of social pictures was associated in both controls and patients with activations in the inferior parietal cortex, precuneus, lateral PFC, caudate, middle temporal cortex, insula and medial PFC. These results are similar to those found in a recent study that investigated the neural correlates of recognition memory for emotional and neutral pictures in healthy controls and patients with schizophrenia.[42] One noticeable difference between our results and those of Lakis and colleagues[42] is the localization of the medial PFC activity during memory retrieval; we found retrieval of social pictures to be associated with DMPFC activity whereas they found retrieval of emotional pictures to be associated with more ventral/orbital PFC activity. This observation is consistent with studies suggesting that the DMPFC is linked to social memory but not to emotional memory.[8,9] In general, the ventral PFC is linked to emotional and representational aspects and the DMPFC to cognitive and evaluational aspects of self-referential stimulus processing.[49–51] Hence, it has been suggested that the role of the DMPFC in social memory involves implicit self-referential processes during encoding and subsequent retrieval.[8] Healthy individuals may have a natural tendency to engage self-referential processes to a greater extent when they observe and analyze social compared with nonsocial information from the environment.[52,53] This is indirectly consistent with our fMRI results showing that the DMPFC was significantly more active during the processing of social versus nonsocial information and that this activation difference was greater in controls than patients. Self-referential processing may boost encoding and subsequent recognition of social stimuli by providing enhanced elaboration and organization to newly learned materials[54,55] and by providing self-relevant category labels that may enhance subsequent recognition by facilitating the reinstatement of encoding conditions at retrieval.[56,57] For instance, one could refer to past personal experiences when encoding social pictures depicting individuals playing on the beach or having a party. These past personal experiences would later be reactivated during subsequent retrieval. Post hoc analyses on encoding data revealed that successful encoding of social pictures in healthy controls was associated with significant activity in several frontal regions, including the DMPFC (Talairach coordinates $x, y, z = -6, 58, 26$; $t = 3.08$, 50 voxels; not reported in the Results section). The DMPFC was not significantly active during successful encoding of nonsocial pictures.

Contrary to healthy controls, patients with schizophrenia did not show enhanced memory for social stimuli compared with

Table 5: Results of the conjunction and interaction analyses for successful retrieval of social information (i.e., old social pictures hits v. new social pictures correctly rejected)*

Analysis; brain region	Talairach coordinates			*t* value	Cluster size
	x	*y*	*z*		
Conjunction†					
Left hemisphere					
Inferior parietal lobule (BA 40)	–40	–55	44	7.13	5651
Middle frontal (BA 10)	–34	50	0	5.46	1069
Middle temporal (BA 21)	–60	–31	–8	5.46	191
Medial frontal (BA 32,10)	–2	38	20	4.58	1006
Caudate	–12	7	8	4.56	274
Middle frontal (BA 8)	–49	12	37	4.18	228
Right hemisphere					
Caudate	7	11	1	6.27	205
Inferior parietal lobule (BA 40)	41	–51	41	5.89	1918
Inferior frontal (BA 13)	29	13	–10	4.63	323
Middle temporal (BA 21)	55	–37	–5	4.00	147
Insula (BA 13)	30	16	–3	3.98	67
Middle frontal (BA 9)	41	35	35	3.53	71
Interaction					
Controls v. patients					
Left hemisphere					
Middle temporal (BA 22)	–54	–35	0	3.21	46
Right hemisphere					
Medial frontal/frontal pole (BA 10)	19	59	15	5.23	139
Patients v. controls					
Right hemisphere					
Postcentral (BA 3)	26	–31	43	3.85	84
Insula (BA 13)	41	–18	–11	3.77	60
Parahippocampal gyrus (BA 30)	17	–36	–4	3.53	44

BA = Brodmann area.
*The cluster size represents the number of voxels. Talairach coordinates represent the peak voxel of each cluster where *x*, *y* and *z* indicate the distance measured in millimetres from the anterior commissure in the sagittal, coronal and horizontal planes, respectively. All clusters of activation were significant at $p < 0.005$, uncorrected for multiple comparisons, with a minimum cluster size of 43 contiguous voxels, corresponding to a false-discovery rate of less than 5% across the whole brain as estimated by Monte Carlo simulation.
†The *t* value reported for the conjunction analysis corresponds to the lowest *t* value between the groups.

nonsocial ones. At the neural level, patients showed significantly reduced activity compared with controls in the middle temporal gyrus, hippocampus, superior frontal gyrus, paracentral lobule and particularly in the DMPFC (i.e., highest *t* value) during retrieval of social stimuli. The activity of the DMPFC was not significantly reduced in patients during retrieval of nonsocial pictures. Notably, the DMPFC activity was also reduced in patients during successful retrieval of social pictures. This suggests that altered DMPFC activity was not the result of impaired memory performance per se, but rather of the use of different cognitive strategies or processes during retrieval. We suggest that an inability to properly activate the DMPFC during retrieval of social stimuli may be linked to reduced contribution or efficiency of self-referential processes in patients with schizophrenia. Recent studies have suggested that these patients are impaired in their ability to process information in reference to self[58,59] and that, for instance, they do not benefit from a memory boost for stimuli processed in a self-referenced manner.[18] Our suggestion is also supported by results of a recent fMRI study that investigated the neural correlates of self-referential processing in patients with schizophrenia.[60] In a study by Bedford and colleagues,[60] participants were shown trait adjectives while being scanned and they were asked to judge whether the traits applied to themselves or another person or whether they contained the letter "a." A significant interaction between diagnosis and self (v. other) processing showed that the DMPFC was the only brain region to show reduced activity in patients compared with controls during self-referential processing.[60] The authors suggested that reduced activity in the DMPFC is best explained by a general failure of patients to engage self-referential processes. However, some of our fMRI results partly contradict this hypothesis. For instance, patients showed greater activity than controls in the precuneus during the processing of social information (i.e., old social pictures – old nonsocial pictures). Meta-analyses of neuroimaging studies on the self suggested a functional distinction among the cortical midline structures (CMS) involved in self-referential processing. On the one hand, they associated the dorsal and anterior part of the CMS to the explicit reasoning, reappraisal and evaluation of self-related stimuli. During both encoding and retrieval of social stimuli, the DMPFC may be crucial in linking the current stimulus to past autobiographical memories and in

Table 6: Results of the conjunction and interaction analyses for the observation of social v. nonsocial information (i.e., old social pictures v. old nonsocial pictures)*

	Talairach coordinates				
Analysis; brain region	*x*	*y*	*z*	*t* value	Cluster size
Conjunction†					
Ventromedial PFC (BA 9,10)	0	50	–15	6.91	554
Left hemisphere					
Middle occipital (BA 19)	–48	–79	6	9.09	8229‡
Middle frontal (BA 9)	–37	15	23	4.56	78
Middle temporal (BA 21)	–53	–16	–8	4.45	205
Amygdala	–21	–10	–13	4.02	76
Right/left hemisphere					
Precuneus (BA 7)	4	–51	42	7.12	3312
Right hemisphere					
Middle occipital (BA 19)	49	–75	3	9.01	8229‡
Middle frontal (BA 9,46)	43	20	26	5.63	1141
Middle temporal (BA 21)	47	–14	–11	5.61	372
Dorsomedial PFC (BA 9,10)	5	53	21	4.53	583
Amygdala	23	–8	–15	4.37	168
Interaction					
Controls > patients					
Right hemisphere					
Dorsomedial PFC (BA 9,10)	18	28	30	4.34	71
Patients > controls					
Left hemisphere					
Precuneus (BA 7)	–12	–79	45	4.18	160
Middle occipital (BA 19)	–28	–86	13	4.19	70
Right hemisphere					
Precuneus (BA 31)	29	–69	22	4.23	53
Postcentral (BA 3)	24	–31	44	3.75	73
Middle occipital (BA 18)	28	–94	13	3.73	65

BA = Brodmann area; PFC = prefrontal cortex.
*The cluster size represents the number of voxels. Talairach coordinates represent the peak voxel of each cluster where *x*, *y* and *z* indicate the distance measured in millimetres from the anterior commissure in the sagittal, coronal and horizontal planes, respectively. All clusters of activation were significant at $p < 0.005$, uncorrected for multiple comparisons, with a minimum cluster size of 43 contiguous voxels, corresponding to a false-discovery rate of less than 5% across the whole brain as estimated by Monte Carlo simulation.
†The *t* value reported for the conjunction analysis corresponds to the lowest *t* value between the groups.
‡These peak voxels belong to the same cluster of activation.

Table 7: Results of the conjunction and interaction analyses for successful encoding (subsequent memory effect) of social and nonsocial information (i.e., pictures subsequently remembered v. pictures subsequently forgotten)*

Analysis; brain region	Talairach coordinates			*t* value	Cluster size
	x	*y*	*z*		
Conjunction, social pictures†					
Left hemisphere					
Fusiform (BA 37)	–34	–47	–15	4.30	1798§
Middle occipital (BA 19)	–44	–82	13	3.53	1798§
Amygdala	–23	–8	–13	3.21	47
Medial Frontal (BA 11)	0	42	–15	3.25	73
Right hemisphere					
Fusiform (BA 37)	39	–51	–10	5.18	2629‡
Amygdala	25	–9	–18	3.21	53
Middle temporal (BA 39)	47	–64	21	4.93	2629‡
Inferior frontal (BA 9)	42	8	26	3.80	289
Conjunction, nonsocial pictures†					
Left hemisphere					
Inferior temporal (BA 37)	–43	–66	–5	5.83	3018¶
Middle occipital (BA 19)	–42	–84	6	5.09	3018¶
Inferior frontal (BA 9)	–41	7	30	4.21	461
Right hemisphere					
Fusiform (BA 37)	35	–43	–11	5.40	2960**
Middle temporal (BA 19)	37	–79	16	4.63	2960**
Middle frontal (BA 46)	46	31	16	3.62	50
Interaction, social pictures					
Controls > patients					
Left hemisphere					
Cingulate (BA 24)	–5	3	23	4.19	206
Thalamus	–10	–8	1	3.23	53
Right hemisphere					
Precentral (BA 4)	61	–6	27	3.80	94
Cingulate (BA 24)	12	3	49	3.39	50
Inferior frontal (BA 47)	36	32	–2	3.13	62
Patients > controls					
Left hemisphere					
Middle frontal (BA 9,10)	–31	33	7	3.90	58
Right hemisphere					
Supramarginal (BA 40)	46	–38	31	3.72	54
Interaction, nonsocial pictures					
Controls > patients					
Left hemisphere					
Inferior parietal (BA 40)	–33	–34	36	3.68	63
Precentral (BA 6)	–35	–4	30	3.53	62
Hippocampus	–26	–33	–8	3.20	56
Right hemisphere					
Superior temporal (BA 38)	36	10	–26	3.42	78
Middle occipital (BA 19)	28	–94	18	3.21	46
Patients > controls					
No significant activation					

BA = Brodmann area.
*The cluster size represents the number of voxels. Talairach coordinates represent the peak voxel of each cluster where *x*, *y* and *z* indicate the distance measured in millimetres from the anterior commissure in the sagittal, coronal and horizontal planes, respectively. All clusters of activation reported were significant at $p < 0.005$, uncorrected for multiple comparisons, with a minimum cluster size of 43 contiguous voxels, corresponding to a false-discovery rate of less than 5% across the whole brain as estimated by Monte Carlo simulation.
†The *t* value reported for the conjunction analysis corresponds to the lowest *t* value between the groups.
‡These peak voxels belong to the same cluster of activation.
§These peak voxels belong to the same cluster of activation.
¶These peak voxels belong to the same cluster of activation.
**These peak voxels belong to the same cluster of activation.

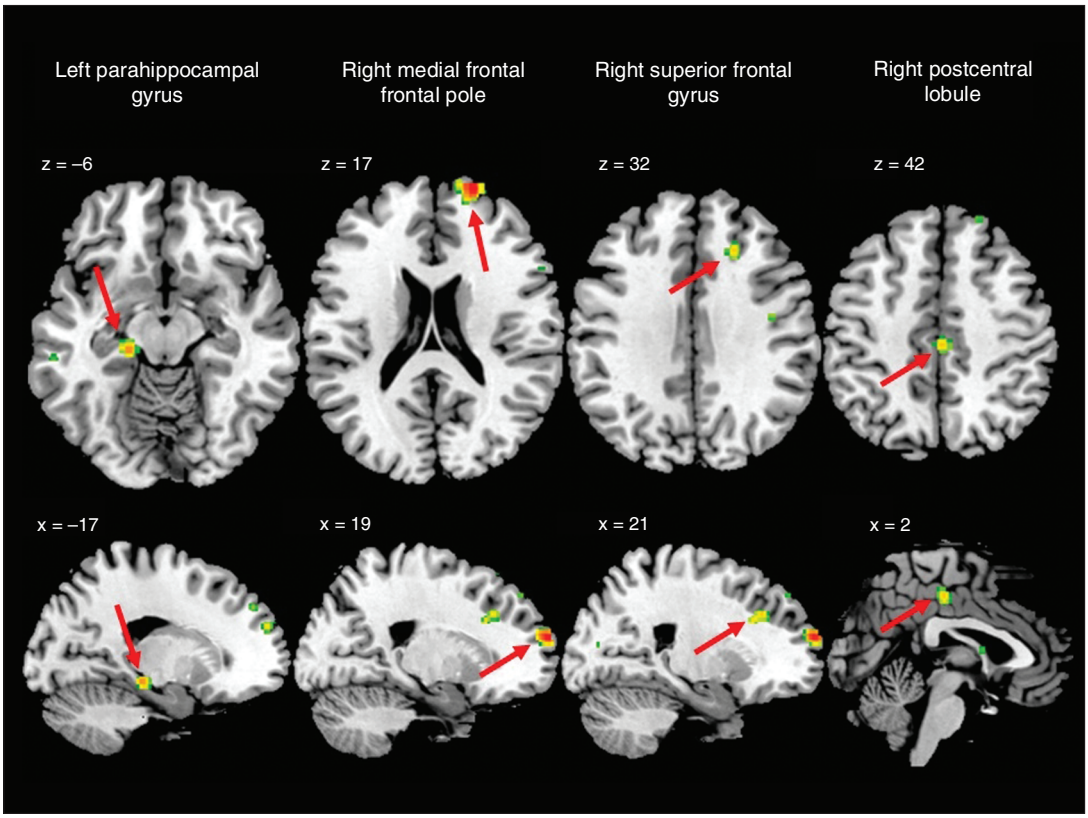

Fig. 3: Brain regions showing greater activity in controls than patients with schizophrenia during the retrieval of old versus new social pictures. Reported activations were thresholded at $p < 0.005$, with an extent threshold of 43 contiguous voxels, corresponding to a false-positive discovery rate of less than 5% across the whole brain.

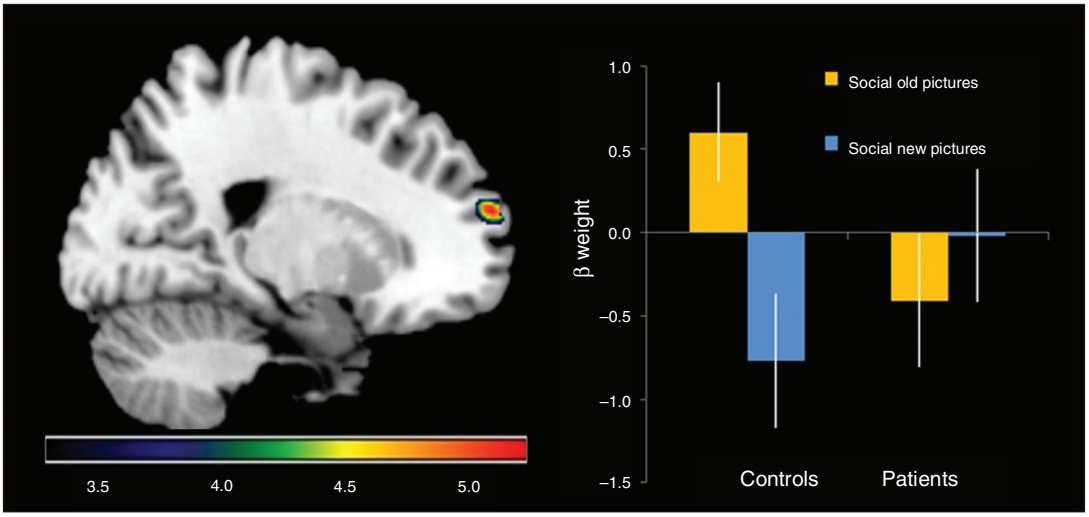

Fig. 4: Parameter estimates (β weights) of the blood oxygen level–dependent signal extracted from a cluster of activation in the dorsomedial prefrontal cortex. This cluster was significantly more active in controls than patients during successful retrieval of social pictures (i.e., social pictures correctly recognized v. social pictures correctly rejected).

deciding whether the link is relevant or whether the stimulus is recognized. On the other hand, the posterior cingulate cortex and adjacent precuneus have been strongly linked to the retrieval of autobiographical memories.[61,62] In our study, memory retrieval of social pictures was associated in both controls and patients with activations in the precuneus and DMPFC among other self-related brain regions. Overall, this suggests that patients are probably, to some extent, engaging in self-referential processing during the encoding or retrieval of social stimuli. However, the formation of a link between autobiographical memories and social stimuli that facilitates memory may not be as strong or efficient in patients with schizophrenia. Greater precuneus activity during social processing in these patients may reflect inefficient overfocus on autobiographical memories, to the detriment of the presented stimulus, which may negatively affect encoding or retrieval processes.

It is still not clear whether patients with schizophrenia fail to engage self-referential processes during encoding of social information, during retrieval or during both steps. Post hoc analyses on encoding data did not show significant activity in the DMPFC during successful encoding of social pictures in patients contrary to controls. However, the DMPFC did not survive our statistical threshold when both groups were directly compared. Hence, we cannot clearly state at this point that the DMPFC is less involved during the encoding of social information in patients with schizophrenia.

Limitations

Some important questions remain to be addressed in future research. Our main suggestion that reduced DMPFC activity in patients is linked to an inability to engage self-referential processing is indirectly supported by findings from several behavioural and fMRI studies, but remains hypothetical. It would be interesting for future studies to replicate our findings with the inclusion of direct measures of self-referential processing. Moreover, we did not find any significant correlations between DMPFC activity and recognition memory performance for social pictures in both groups. Hence, the causality in brain–behaviour relations needs to be demonstrated. In addition, even if our social and nonsocial picture conditions were equated for the number of emotional pictures, our study does not rule out the possibility that emotion interacted differently with memory between social and nonsocial conditions. We did not examine social versus nonsocial stimuli within emotional categories partly because we did not have enough stimuli per run at retrieval to model 12 conditions: 2 content conditions (social, nonsocial) × 3 emotion conditions (positive, negative, neutral) × 2 memory conditions (old, new). A modified version of our task that would include additional pictures could allow a more refined investigation of emotion × content interactions. In addition, our protocol defined social pictures as those showing at least 1 human being, whereas the nonsocial ones were characterized by the absence of any human being. Pictures with human content represent only 1 type of social stimuli, which is far from emulating the full complexity associated with real life social interactions (e.g., prosody, body and facial movements, social context, environment). It is possible that patients with schizophrenia are impaired for aspects of social interactions/situations that are not well represented by pictures with human content (i.e., prosody, biological motion). Future neuroimaging studies should use more complex and ecological social stimuli, such as shorts videos. Another limitation of this study involves antipsychotic mediation. All but 3 patients were taking antipsychotic medications, which may have altered both the behavioural performance at the picture recognition memory task and brain activity. Using a similar paradigm in unmedicated patients will allow researchers to avoid the potential confound of pharmacological treatment.

Conclusion

This is one of few studies that investigated social memory in patients with schizophrenia. Our experiment yielded 2 major findings: first, patients did not show a memory boost for social information, and second, patients did not activate the DMPFC as much as controls during memory retrieval of social information, which could be related to reduced involvement of self-referential processes. Our fMRI results contribute in mapping more precisely the neural disturbances associated with social memory impairment in patients with schizophrenia by identifying the DMPFC as a key brain region. In conjunction with other imaging studies on social memory in patients with schizophrenia, our study may facilitate the development of innovative treatments, such as repetitive or deep transcranial magnetic stimulation techniques, that target abnormal brain regions (e.g., DMPFC). Improving social memory through these new treatment approaches may improve social cognitive abilities and ultimately social functioning in patients with schizophrenia.

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